Passive Smoking and Middle Ear Effusion Among Children in Day Care

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ABSTRACT. One hundred thirty-two children who attended a research day-care center were studied to determine whether passive tobacco smoke exposure was associated with an increased rate of otitis media with effusion or with an increased number of days with otitis media with effusion during the first 3 years of life. Based on preliminary studies, a serum cotinine concentration of ≥2.5 ng/mL was considered indicative of exposure to tobacco smoke. Otitis media with effusion was diagnosed using pneumatic otoscopy by nurse practitioners and pediatricians who reviewed the children's health status each weekday. The 87 children with serum cotinine concentrations ≥2.5 ng/mL had a 38% higher rate of new episodes of otitis media with effusion during the first 3 years of life than the 45 children with lower or undetectable serum cotinine concentrations (incidence density ratio = 1.38, 95% confidence interval 1.21 to 1.56). The average duration of an episode of otitis media with effusion was 28 days in the children with elevated cotinine concentrations and 19 days in the children with lower cotinine concentrations ($P < .01$). It is estimated that 8% of the cases of otitis media with effusion in this population and 17.6% of the days with otitis media with effusion may be attributable to exposure to tobacco smoke. ***Pediatrics* 1992;90:228–232; *otitis media, passive smoking, tobacco, day care.***

Numerous studies have shown that infants with smoking mothers have a greater risk of lower respiratory illness in the first year of life.[1–6] It is unclear, however, whether exposure to environmental tobacco smoke increases children's risk of upper respiratory illness including otitis media with effusion (OME).

An association has been reported between chronic middle ear effusion and tobacco smoke exposure. Two case-control studies[7,8] found that elementary school children who underwent tympanostomy tube placement were more likely to have lived in households where cigarettes were smoked. Neither study evaluated the relationship between passive smoking and frequency of OME or any measure of OME burden during the first 3 years of life. Also, in these studies, the estimate of a child's passive tobacco smoke exposure was based on parents' self-reports of their usual cigarette consumption. This may be an imprecise estimate, however, because the amount of tobacco smoke products actually absorbed by the child could vary considerably depending on the amount of smoke present in the environment, the child's proximity to the source of the smoke, and the room's ventilation characteristics. In the current study, a biochemical measure of exposure to tobacco smoke, serum cotinine concentration, was used.

The present study was designed to determine whether the children in a day-care center with elevated serum cotinine concentrations had more episodes of middle ear effusion in the first 3 years of life or more days with middle ear effusion than the children with absent or lower concentrations of cotinine in serum. Our a priori hypothesis was that children with serum cotinine concentrations ≥2.5 ng/mL would have an increased rate of OME in the first 3 years of life compared with children with serum cotinine concentrations <2.5 ng/mL.

METHODS

Study Setting

Children were selected from those enrolled in the day-care project of the Frank Porter Graham Child Development Center, a multidisciplinary research program.[9] Research on respiratory health has been an integral aspect of the day-care center's program since its inception in 1964, and general aspects of infection and illness documentation have been described previously.[10–12] Children were generally admitted to this day-care project as soon as possible after 6 weeks of age. They spent 8 hours a day, 5 days a week at the center and returned to their homes each evening. Smoking was not permitted in child-care areas of the center.

Study Design

We identified study children from among the 200 who had entered the center between 1964 and 1983. Children who were eligible for inclusion in this study met the following four criteria: (1) enrolled in the day-care center before 6 months of age, (2) remained at the day-care center for 18 months or more during the first 3 years of life, (3) spent no more than 4 consecutive months away from the day-care center during the first 3 years of life, and (4) had serum available for analysis. These eligibility criteria ensured that the children in the study were all under observation during the period of greatest risk for OME.[13]

One hundred thirty-two children met the eligibility criteria for this study. Of the 61 children who were ineligible, 27 entered after age 6 months, 30 were enrolled for less than 18 months prior to their third birthday, 4 were absent for more than 4 consecutive months, and 7 had no serum available for analysis because it had already been used for other purposes.

Detection and Diagnosis of Otitis Media With Effusion

Children's health status was reviewed each weekday by a full-time nurse on site at the day-care center; physical examinations were performed by pediatricians or nurse practitioners when any symptoms or signs of respiratory illness were present.

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Middle ear effusion, the outcome of interest, was measured using pneumatic otoscopy. Clinicians made the diagnosis when the mobility of the tympanic membrane was markedly reduced or absent or when middle ear fluid was seen. Precise differentiation between purulent and nonpurulent effusions was not possible because tympanocenteses were not performed. An episode of OME was defined as a new effusion in one or both ears previously documented to have been free of fluid. All children in whom otitis media with effusion was diagnosed were treated with antibiotics by the nurse practitioners and pediatricians staffing the day-care center. Physical examinations were performed biweekly after diagnosis of middle ear effusion until the effusion had cleared. The shortest interval between two new onsets of OME was 2 weeks.

In this study, pneumatic otoscopy was not reinforced by tympanometry. Observer variability was controlled by limiting the number of clinicians who performed the examinations to two pediatricians and two nurse practitioners, all of whom were specially trained in pneumatic otoscopy.

Diagnosis of Respiratory Infection

Cultures of the upper respiratory tract for the detection of viruses and bacteria were obtained at the onset of each respiratory illness throughout the study period (1964 through 1983). Samples of respiratory secretions were obtained by performing a saline nasal wash and a throat swab. For this study, we were primarily interested in infection with three viruses (respiratory syncytial virus, adenoviruses, and influenza viruses) and colonization with two bacteria (*Haemophilus influenzae* and *Streptococcus pneumoniae*), because these had been demonstrated in a previous study[14] to be linked epidemiologically to the occurrence of OME. Viral infection (the percent of first illness cultures positive for adenoviruses, respiratory syncytial virus, or influenza viruses) and bacterial colonization (the percent of first illness cultures positive for *S pneumoniae* or *H influenzae*) rates were calculated for each child.

Measurement of Exposure

The measure of exposure to tobacco smoke was the child's serum cotinine concentration. Cotinine, the major metabolite of nicotine, is specific for tobacco exposure, is produced only in vivo, has a circulating half-life of 19 to 40 hours,[15,16] and can be measured by radioimmunoassay at very low concentrations.[16] In a previous study of a subset of these children, the serum cotinine concentration was significantly associated with a history of smoking in the home.[17]

As part of ongoing studies of respiratory diseases, each of the children enrolled in the day-care center had venous blood drawn in the spring and again in the fall of each year and placed in storage at −20°C. To determine each child's exposure to tobacco smoke, the serum sample drawn nearest the child's first birthday was thawed, an aliquot removed, and the sample shipped to the American Health Foundation in Valhalla, NY, where a radioimmunoassay for cotinine was performed without knowledge of the child's exposure status or illness history.[18]

On the basis of these serum cotinine concentrations, the 132 children were separated into two groups. Receiver operator characteristic curve analysis[19] of data obtained from our previous studies[17,20] had determined that a cutoff point of 2.5 ng/mL would minimize the sum of the false-negative and false-positive test results when using the serum cotinine to differentiate the children living in homes with at least one smoker from those who were living in homes where no one smoked. Therefore, those children with serum cotinine concentrations ≥2.5 ng/mL were classified as "exposed," and those with serum cotinine concentrations less than 2.5 ng/mL were classified as "unexposed" to tobacco smoke.

Measurement of Extraneous Variables

Each child's medical record was reviewed to obtain information on potential confounding variables including prematurity, congenital anomalies, breast-feeding (defined as one or more days of breast-feeding), socioeconomic status (as measured by the Hollingshead index),[21] atopic family history (as measured by parental report at admission examination of asthma or hay fever in immediate family), and history of OME prior to day-care center enrollment.

Statistical Tests

During the time OME is present, a child is not at risk of developing OME. For that reason, the incidence density was used to measure the frequency of OME. The incidence density of OME was calculated by dividing the total number of new cases of OME during the period of observation by the total number of child-days at risk during that period.[22] This denominator was calculated by subtracting from each child's total time under observation the number of days with OME. To test the null hypothesis that there was no association between exposure to tobacco smoke and the incidence density of OME, a large sample χ^2 test was constructed by using the normal approximation to the binomial distribution.[23] We used the test-based confidence interval suggested by Miettinen[22] to calculate the confidence intervals around the point estimate of the incidence density ratio. To test the overall association, stratified by potential confounding variables, the Mantel-Haenszel test statistic for density follow-up studies was used.[22] A one-tailed Kolmogorov-Smirnov two-sample test was used to test whether the distributions of otitis media incidence or prevalence rates were higher in the exposed than in the unexposed children.[24] Linear regression analysis was performed to identify significant predictors of the duration of otitis media.

RESULTS

The 132 children in this study included 71 boys and 61 girls; there were 100 blacks, 30 whites, and 2 children of mixed race. During the first 3 years of life, these 132 children were enrolled in the Frank Porter Graham Child Development Center for an average of 984 days (range 568 to 1075 days). The total length of time the children in the exposed and unexposed groups were enrolled in the day-care center between entry and age 3 was not significantly different (1001 days vs 976 days in the exposed and unexposed groups, respectively, $P = .15$). However, their child-days at risk differed significantly (752 vs 845 in the exposed and unexposed groups, respectively, $P = .01$).

Seventy-eight (59%) of the 132 children had detectable cotinine in their blood. The age at which the blood was drawn ranged between 4 months and 6.5 years with a mean age of 1.4 years. The cutoff point of 2.5 ng/mL resulted in the classification of 45 children as exposed and 87 children as unexposed to tobacco smoke.

Blood samples were obtained during the colder months (September through February) from 24 exposed children (53%) and 58 unexposed children (67%). Blood samples were obtained during the warmer months (April through August) from 21 exposed children (47%) and 29 unexposed children (33%).

Occurrence of Otitis Media With Effusion

Overall, in both groups combined, study children had an average of 7.78 (SD = 4.55) new episodes of OME per child in 984 days (2.9 episodes per year). Only one child (in the unexposed group) experienced no episode of OME in the first 3 years of life. The 45 exposed children experienced an average of 8.7 episodes of OME in the first 3 years of life, while the 87 unexposed children experienced 7.3 episodes in that period ($P = .08$).

Table 1 shows the incidence density of OME in the exposed and unexposed groups. The 45 exposed children experienced 393 episodes of otitis media in the first 3 years of life (incidence density = 0.0119/child-day), and the 87 unexposed children experienced 634

episodes in that period (incidence density = 0.0086/child-day). The resulting incidence density ratio was 1.38 (95% confidence interval 1.21 to 1.56). During the first year of life, the incidence density ratio for OME was 1.39 with a 95% confidence interval extending from 1.15 to 1.69 (Table 2).

The Figure illustrates the incidence density ratios and 95% confidence intervals for each of the first 3 years of life. Tobacco smoke exposure seemed to have its greatest effect in the first 2 years of life.

To examine further the differences in OME experience between exposed and unexposed children, a second, more conservative approach (a one-tailed Kolmogorov-Smirnov two-sample test) was used. This nonparametric test is used to test the hypothesis that two groups of observations have identical distributions. The distribution of otitis media attack rates in the exposed children was not significantly different than the distribution of otitis media attack rates in the unexposed children ($P > .05$).

Duration of Middle Ear Effusion

Consistent recording of OME duration data was initiated in 1968; 106 children had complete data on this variable. The 41 exposed children had a mean total duration of 268 days (an average of 28 days per effusion) while the 65 unexposed children had a mean total duration of 170 days (an average of 19 days per effusion) ($P < .01$). The distribution of total otitis media durations for the exposed children was significantly longer than that for the unexposed children ($P < .05$ by one-tailed Kolmogorov-Smirnov two-sample test).

Using linear regression analysis, we identified two significant predictors of the duration of middle ear effusion in this sample of 106 children: the child's cotinine concentration ($P = .0001$) and the age at which the child's first episode of OME occurred ($P = .03$). Those children with higher cotinine concentrations and earlier first episodes tended to have longer durations of middle ear effusion.

Because the highest frequency of middle ear effusion occurred in the 18 months between 6 and 24 months of age, and because all 132 children were enrolled during that time, subsequent analyses were restricted to this interval. Furthermore, because the discrepancy in duration of middle ear effusion could inflate the incidence density ratio, for all further analyses a standard duration of 7 days was subtracted for each episode of OME in children in both the exposed and unexposed groups.

Table 3 shows the incidence density of OME in the exposed and unexposed groups. The incidence density ratio is 1.24 with a 95% confidence interval extending from 1.07 to 1.43. This point estimate is slightly lower than that during the first year of life (1.39) and the second year of life (1.62) because of the different way in which the denominator was calculated. The point estimate of 1.24 is almost certainly an underestimate because of the use of the standard duration.

Potential Confounding Variables

Analyses were performed after stratifying for each potential confounding variable.[25] Mantel-Haenszel test statistics and P values were computed for each stratum. The overall association between serum cotinine concentration and OME remained significant after controlling individually for each of these potential confounding variables: gender, race, viral infection rate, bacterial colonization rate, coryza rate, atopic disease, breast-feeding, kerosene heater use in home, woodstove use in home, diagnosing clinician, and documentation of tympanic membrane mobility. Be-

TABLE 1. Incidence Density for Otitis Media With Effusion During the First 3 Years of Life According to Tobacco Smoke Exposure

	Exposed (n = 45)	Unexposed (n = 87)	Total (n = 132)
New episodes of otitis media with effusion	393	634	1 027
Child-days at risk	33 036	73 328	106 364
Incidence density	0.0119	0.0086	0.0097

Incidence density in exposed/incidence density in unexposed = 1.38 (95% confidence interval 1.21 to 1.56). Incidence density in exposed − incidence density in unexposed = 0.003 (95% confidence interval 0.002 to 0.005).

TABLE 2. Incidence Density for Otitis Media With Effusion During the First Year of Life According to Tobacco Smoke Exposure

	Exposed (n = 45)	Unexposed (n = 87)	Total (n = 132)
New episodes of otitis media with effusion	168	279	447
Child-days at risk	8 877	20 535	29 412
Incidence density	0.0189	0.0136	0.015

Incidence density in exposed/incidence density in unexposed = 1.39 (95% confidence interval 1.15 to 1.69).

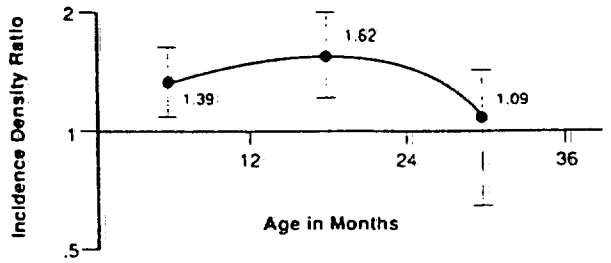

Figure. Incidence density ratios (logarithmic scale) and 95% confidence intervals for otitis media with effusion during each of the first 3 years of life.

TABLE 3. Incidence Density for Otitis Media With Effusion (Age 6 Months Through 24 Months) According to Tobacco Smoke Exposure

	Exposed (n = 45)	Unexposed (n = 87)	Total (n = 132)
New episodes of otitis media with effusion	318	504	822
Child-days at risk†	21 909	43 035	64 944
Incidence density	0.0145	0.0117	0.013

Incidence density in exposed/incidence density in unexposed = 1.24 (95% confidence interval 1.07 to 1.43). Incidence density in exposed − incidence density in unexposed = 0.003 (95% confidence interval 0.001 to 0.005).

† Standard duration of 7 days subtracted for each episode of otitis media with effusion.

cause only one child in the study group had tympanostomy tubes placed, this variable was not included among the potential confounding variables.

Population Attributable Fraction

The information in Table 3 can be used to calculate the fraction of OME cases in the population ("population attributable fraction") that might be preventable by eliminating children's tobacco smoke exposure. The risk difference of 0.003 is multiplied by the prevalence of smoking (which was about 38% in North Carolina at the end of this study) to derive the population attributable risk of 0.001. From the same table, the total rate of OME is seen to be 0.013. Hence the population attributable fraction is estimated to be 0.001/0.013 or 8%.

Likewise, we can estimate the number of days with otitis media which may have been preventable. An estimated 3565 days, or 17.6% of the total days with OME, may have been prevented if tobacco smoke exposure were eliminated.

DISCUSSION

The children in this study with elevated serum cotinine concentrations had a longer average duration of middle ear effusion than those with absent or lower serum cotinine concentrations. The difference in OME duration is especially notable insofar as the duration of illness may be a better measure of the burden of otitis media than the number of discrete episodes.

This study is unique with respect to both the measurement of exposure to tobacco smoke and the measurement of otitis media with effusion. The use of serum cotinine concentration, an objective measure of tobacco smoke exposure, may have avoided the potential misclassification inherent in parental reporting of smoking behavior. The prospective documentation of OME over the first 3 years of life at the Frank Porter Graham Child Development Center is also independent of the parental decision to bring the child to a clinician for a physical examination.

Our findings are consistent with the findings of Iversen et al,[26] who studied children between 0 and 7 years of age in Danish day-care centers and demonstrated an overall odds ratio of 1.6 (95% confidence interval from 1.00 to 2.5) for parental smoking and middle ear effusion as measured by tympanometry. That study reported point prevalence data in relation to parental reports of smoking behavior and estimated the overall fraction of middle ear effusion attributable to parental smoking to be 15%. Strachan et al[27] estimated that about one third of the cases of middle ear effusion in 6- to 7-year-old schoolchildren were attributable to passive smoking. The current study, using incidence density data, estimates the attributable fraction to be 8% in preschool children in day care.

When interpreting these results, it should be noted that because the children in this day-care center were in a smoke-free environment for 8 hours each day, our estimate of the difference in OME risk related to tobacco smoke exposure is likely to be an underestimate of the risk in the home setting. Had we compared children being cared for at home by smoking parents to those living in smoke-free homes, we might have demonstrated an even larger risk difference.

It is important to note that the use of the incidence density ratio does not take into account the fact that episodes of otitis media experienced by an individual child are not independent of one another. A more conservative test, the Kolmogorov-Smirnov test, did not verify that the difference between the distributions of attack rates in exposed and unexposed children was significant. In view of these conflicting results, we believe that any difference in the number of episodes of otitis media with effusion is probably small. However, the Kolmogorov-Smirnov test provided additional evidence that the difference in duration of otitis media between the exposed and unexposed children was significant.

The possibility of misclassification bias must be addressed. Since the pediatricians and nurse practitioners who diagnosed and treated each episode of otitis media were unaware of the study hypothesis, it is very unlikely that diagnosis of OME would have differed according to the exposure status of the child. Also, there had been no literature suggesting an association between tobacco smoke exposure and middle ear disease until 1983,[7] and data collection took place between 1964 and 1984. Furthermore, even if the clinicians had been aware of that potential association, they were unaware of the child's exposure status unless they were familiar with the child's parents' smoking habits. Although misclassification of exposure may have occurred on the basis of a single cotinine determination, it is very unlikely to have differed according to the disease history of the child. Our estimates of duration of OME were based on biweekly examinations of the study children after diagnosis. Although this is a somewhat imprecise measure, it is not likely to have differed according to the exposure status of the child. All of these possible sources of misclassification would have made it less likely that this study would demonstrate a difference between the exposed and unexposed groups, thus serving to strengthen these results.

Other researchers have documented that children in day-care settings have an increased incidence of otitis media.[28–32] This study was not designed to address that issue. Our results do demonstrate a higher incidence of otitis media than was reported by Teele and his colleagues.[33] They followed 2565 children for the first 3 years of life and found that one third of them had three or more episodes of otitis media, while 29% never had any otitis media in the first 3 years of life. Thus it is doubtful that generalizations can be made from our results to children who are not attending day-care centers. Our study site was chosen for convenience; population-based studies are needed to define further this apparent association.

There are several possible mechanisms by which tobacco smoke might influence the occurrence of middle ear effusion. Experimental data show that smoke exposure can result in goblet cell hyperplasia and mucus hypersecretion in the respiratory tract,[34] possibly including the eustachian tube and middle ear. This might lead to functional obstruction of a child's eustachian tube, especially when the exposure

occurs during a symptomatic viral upper respiratory illness, which could result in OME. Another possible mechanism is that tobacco smoke may diminish ciliary function. Some animal evidence indicates that short-term exposure to cigarette smoke causes ciliostasis and decreased mucociliary transport.[35] A third possible mechanism is that cigarette smoke and certain viral infections both alter the phagocytic antibacterial defenses of the respiratory tract, perhaps synergistically. This may lead to increased bacterial colonization and subsequently more otitis media.

Otitis media with effusion is an important public health problem. It is the most common illness diagnosed in US pediatricians' offices.[36] In 1980, otitis media accounted for 5 million office visits for children younger than age 3 in the United States.[37] It is estimated that $1 billion to $2 billion are spent on otitis media each year in the United States.[37] Since OME is such a common disease, prevention of even a small proportion of illness-days by limiting the exposure of children to environmental tobacco smoke could have a large public health impact.

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REFERENCES

1. Harlap S, Davies AM. Infant admissions to hospital and maternal smoking. *Lancet*. 1974;1:529–532
2. Colley JRT, Holland WW, Corkhill RT. Influence of passive smoking and parental phlegm on pneumonia and bronchitis in early childhood. *Lancet*. 1974;2:1031–1034
3. Rantakallio P. Relationship of maternal smoking to morbidity and mortality of the child up to the age of five. *Acta Paediatr Scand*. 1978;67:621–631
4. Fergusson DM, Horwood LJ, Shannon FT. Parental smoking and respiratory illness in infancy. *Arch Dis Child*. 1980;55:358–361
5. US Dept of Health and Human Services. *The Health Consequences of Involuntary Smoking: A Report of the Surgeon General*. Washington, DC: US Government Printing Office; 1986:38–59. Dept of Health and Human Services publication CDC 87-8398
6. National Research Council. *Environmental Tobacco Smoke: Measuring Exposure and Assessing Health Effects*. Washington, DC: National Academy Press; 1986:188–212
7. Kraemer MJ, Richardson MA, Weiss NS, et al. Risk factors for persistent middle-ear effusions. *JAMA*. 1983;249:1022–1025
8. Black N. The aetiology of glue ear: a case-control study. *Int J Pediatr Otorhinolaryngol*. 1985;9:121–133
9. Ramey CT, Campbell FA. Preventive education for high-risk children: cognitive consequences of the Carolina Abecedarian Project. *Am J Ment Defic*. 1984;5:515–523
10. Loda FA, Glezen WP, Clyde WA Jr. Respiratory disease in group day care. *Pediatrics*. 1972;49:428–437
11. Henderson FW, Collier AM, Clyde WA Jr, Denny FW. Respiratory-syncytial-virus infections, reinfections and immunity: a prospective, longitudinal study in young children. *N Engl J Med*. 1979;300:530–534
12. Roberts JE, Sanyal MA, Burchinal MR, Collier AM, Ramey CT, Henderson FW. Otitis media in early childhood and its relationship to later verbal and academic performance. *Pediatrics*. 1986;78:423–430
13. Paradise JL. Otitis media in infants and children. *Pediatrics*. 1980;65:917–943
14. Henderson FW, Collier AM, Sanyal MA, et al. A longitudinal study of respiratory viruses and bacteria in the etiology of acute otitis media with effusion. *N Engl J Med*. 1982;306:1377–1383
15. Benowitz NL, Kuyt F, Jacob P, Jones RT, Osman AL. Cotinine disposition and effects. *Clin Pharmacol Ther*. 1983;34:604–611
16. Langone JJ, Gjika HB, VanVunakis H. Nicotine and its metabolites: radioimmunoassays for nicotine and cotinine. *Biochemistry*. 1973;12:5025–5030
17. Pattishall EN, Strope GL, Etzel RA, Helms RW, Haley NJ, Denny FW. Serum cotinine as a measure of tobacco smoke exposure in children. *AJDC*. 1985;139:1101–1104
18. Haley NJ, Hoffmann D. Analysis for nicotine and cotinine in hair to determine cigarette smoker status. *Clin Chem*. 1985;31:1598–1600
19. Metz CE. Basic principles of ROC analysis. *Semin Nucl Med*. 1978;8:283–298
20. Etzel R, Pattishall E, Abernathy L, Haley N, Collier A, Henderson F. Serum cotinine measures passive smoking in young children. *Clin Res*. 1984;32:879A
21. Hollingshead AB, Redlich FC. *Social Class and Mental Illness*. New York, NY: John Wiley; 1958
22. Miettinen OS. Estimability and estimation in case-referent studies. *Am J Epidemiol*. 1976;103:226–235
23. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic Research: Principles and Quantitative Methods*. Belmont, CA: Lifetime Learning Publications; 1982
24. Steel RGD, Torrie JH. *Principles and Procedures of Statistics: A Biometrical Approach*. 2nd ed. New York, NY: McGraw Hill; 1980
25. Miettinen OS, Cook EF. Confounding: essence and detection. *Am J Epidemiol*. 1981;114:593–603
26. Iversen M, Birch L, Lundqvist GR, Elbrond O. Middle ear effusion in children and the indoor environment: an epidemiological study. *Arch Environ Health*. 1985;40:74–79
27. Strachan DP, Jarvis MJ, Feyerabend C. Passive smoking, salivary cotinine concentrations, and middle ear effusion in 7 year old children. *Br Med J*. 1989;298:1549–1552
28. Strangert K. Otitis media in young children in different types of day-care. *Scand J Infect Dis*. 1977;9:119–123
29. Lundgren K, Ingvarsson L. Epidemiology of acute otitis media in children. *Scand J Infect Dis*. 1983;39(suppl):19–25
30. Vinther B, Brahe Pedersen C, Elbrond O. Otitis media in childhood: sociomedical aspects with special reference to day-care conditions. *Clin Otolaryngol*. 1984;9:3–8
31. Fleming DW, Cochi SL, Hightower AW, Broome CV. Childhood upper respiratory tract infections: to what degree is incidence affected by day-care attendance? *Pediatrics*. 1987;79:55–60
32. Froom J, Culpepper L. Otitis media in day-care children: a report from the international primary care network. *J Fam Pract*. 1991;32:289–294
33. Teele DW, Klein JO, Rosner BA. Epidemiology of otitis media in children. *Ann Otol Rhinol Laryngol*. 1980;89(suppl 68):5–6
34. US Dept of Health and Human Services. *The Health Consequences of Smoking: Chronic Obstructive Lung Disease. A Report of the Surgeon General*. Rockville, MD: Office on Smoking and Health; 1984:292. Dept of Health and Human Services publication (PHS) 84-50205
35. Wanner A. State of the art: clinical aspects of mucociliary transport. *Am Rev Respir Dis*. 1977;116:73–125
36. Ezzati T. Ambulatory medical care rendered in pediatricians' offices during 1975. *Advance Data From Vital and Health Statistics*. Rockville, MD: Public Health Service; 1977. Dept of Health, Education, and Welfare publication (HRA) 77-1250
37. Lohr KN, Beck S, Kamberg CJ, Brook RH, Goldberg GA. *Measurement of Physiologic Health for Children: Middle Ear Disease and Hearing Impairment*. Santa Monica, CA: The Rand Corporation; 1984